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Rh-Catalyzed Asymmetric Hydrogenation of γ-Phthalimido-Substituted α,β-Unsaturated Carboxylic Acid Esters: An Efficient Enantioselective Synthesis of β-Aryl-γ-amino Acids

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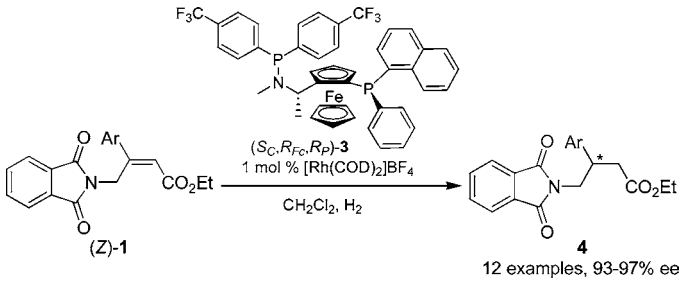
ABSTRACT



A series of chiral β-aryl-γ-amino acid ester derivatives were synthesized in high enantioselectivities (93–97% ee) via the Rh-catalyzed asymmetric hydrogenation of γ-phthalimido-α,β-unsaturated carboxylic acid esters using highly modular chiral BoPhoz-type phosphine–aminophosphine ligands. The method has been applied successfully to the synthesis of several chiral pharmaceuticals including (*R*)-baclofen and (*R*)-rolipram with high enantioselectivities.

Chiral γ-amino acids and their derivatives, in particular those analogues bearing substituents at the β-position, have been the subject of extensive investigations in past decades for their promising therapeutic use in the treatment of a range of central nervous system disorders and their useful application as building blocks in organic synthesis.[1] Although some catalytic asymmetric syntheses of β-substituted γ-amino acid derivatives have been reported,[2] the development of new and efficient catalytic asymmetric synthetic methods with properties superior to their predecessors for enantioselective synthesis of γ-amino acid derivatives remains a significant challenge. Given its inherent efficiency and atom economy, the catalytic asymmetric hydrogenation of γ-dehydroamino acid derivatives would seem to be an ideal approach to prepare enantiopure γ-amino acids. Indeed, such methods are among the most studied and widely applied for the

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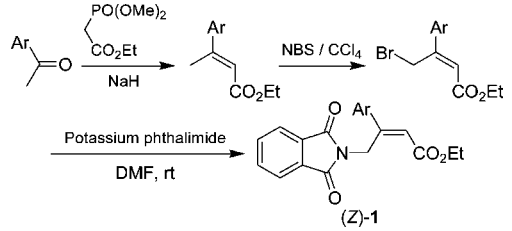
enantioselective preparation of α- and β-amino acids.[3] To the best of our knowledge, however, the catalytic enantioselective hydrogenation of γ-amino acid dehydro precursors with chiral metal complexes remains a rarely explored area.[4] Only one successful example was reported by the researchers from Pfizer Inc., in which a highly efficient Rh-catalyzed hydrogenation of a cyano (CN)-substituted precursor to pregabalin, a chiral β-*i*-Bu-substituted γ-amino acid pharmaceutical, was developed.[5] Herein we report the first highly enantioselective synthesis of a series of chiral β-aryl-γ-amino acid ester derivatives by a rhodium-catalyzed asymmetric hydrogenation of (*Z*)-3-aryl-4-phthalimidobut-2-enoates with highly modular Bophoz-type phosphine−aminophosphine ligands.

Prochiral γ-dehydroamino acid esters, ethyl (*Z*)-3-aryl-4-phthalimidobut-2-enoates, can be easily prepared from aryl ketones through a three-step transformation as outlined in Scheme 1. The high crystallinity conferred by the phthalimido group makes the purification of the rude substrates convenient. With easy access to the substrates, the key to achieving high enantioselectivity in the hydrogenation of these γ-dehydroamino acid esters, therefore, is to find an efficient catalyst. We focused our efforts on searching for an appropriate chiral phosphorus ligand for their demonstrated track record at effecting Rh-catalyzed asymmetric hydrogenations. Exploratory ligand screening employed ethyl (*Z*)-4-phthalimido-3-phenylbut-2-enoate **1a** as the standard substrate and a diverse array of chiral phosphorus-containing ligands, which are commercially available or developed within our research group. A few representative ligands screened are shown in Figure 1.

Unlike the hydrogenation of α- and β-dehydroamino acid esters, the hydrogenation of ethyl 4-phthalimido-3-phenylbut-2-enoate **1a** proved to be highly difficult. The data summarized in Table 1 revealed that most of the phosphorus-ligand/Rh complexes screened, which have proved to be highly efficient for the asymmetric hydrogenation of functionalized olefins, gave poor results in this hydrogenation reaction of **1a**. For example, bidentate DuPhos, BINAP, TaniaPhos, and PPFAPhos gave low to moderate enantiose-

Scheme 1. Synthesis of γ-Dehydroamino Acid Esters (*Z*)-**1**



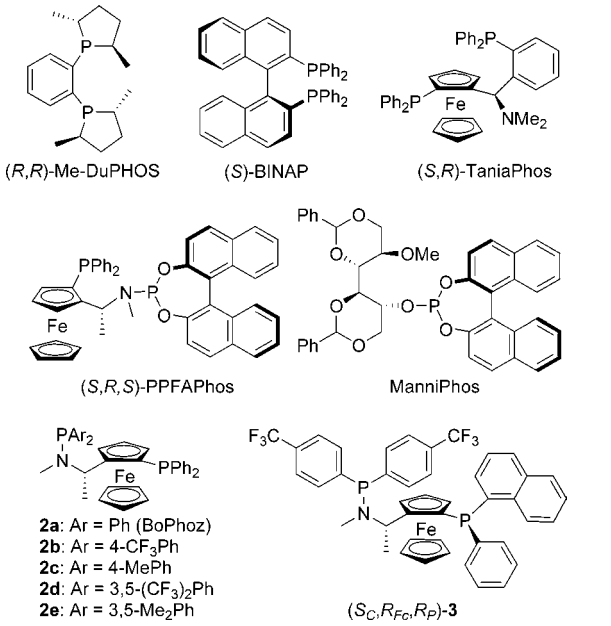
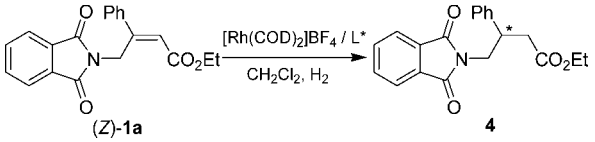


Figure 1. Structure of some representative ligands for asymmetric hydrogenation.

Table 1. Asymmetric Hydrogenation of Ethyl (*Z*)-4-Phthalimido-3-phenylbut-2-enoate **1a**[a]



entry	ligand	solvent	convn (%)	ee (%)
1	DuPHOS	CH_2Cl_2	91	70
2	BINAP	CH_2Cl_2	62	16
3	TaniaPhos	CH_2Cl_2	>95	40
4	PPFAPhos	CH_2Cl_2	83	4
5	ManniPhos	CH_2Cl_2	–	–[b]
6	BoPhoz **2a**	CH_2Cl_2	>95	88
7	**2a**	$Cl(CH_2)_2Cl$	>95	88
8	**2a**	MeOH	83	11
9	**2a**	toluene	33	15
10	**2a**	THF	51	50
11	**2a**	*i*-PrOH	91	75
12	**2b**	CH_2Cl_2	>95	92
13	**2c**	CH_2Cl_2	>95	87
14	**2d**	CH_2Cl_2	>95	93
15	**2e**	CH_2Cl_2	>95	86
16	(S_C,R_{Fc},R_P)-**3**	CH_2Cl_2	>95	95
17	(S_C,R_{Fc},R_P)-**3**	CH_2Cl_2	>95	93[c]

[a] All reactions were carried out with 0.25 mmol of substrate at room temperature under a H_2 pressure of 60 atm in 2 mL of the indicated solvent for 24 h with a substrate/$[Rh(COD)_2]BF_4$/ligand ratio of 1/0.01/0.011. Conversions were determined by ^1H NMR. The ee values were determined by HPLC on a chiral column (Chiralpak AD). [b] Not determined because of low reactivity. [c] 10 atm of H_2, 50 °C, 24 h.

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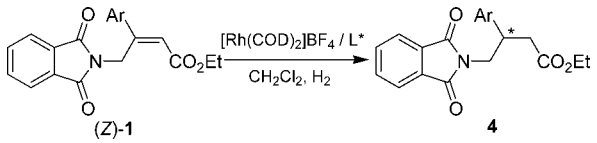
lectivity although high conversions were obtained in some cases (Table 1, entries 1−4), while monodentate ManniPhos showed no activity for this reaction (Table 1, entry 5). To our delight, we found that the Rh/Me-BoPhoz complex afforded nearly full conversions and high enantiomeric excess (88% ee, Table 1, entry 6). Subsequent experiments in an effort to attain higher enantioselectivies by optimizing the reaction conditions proved unfruitful. As shown in Table 1, a strong solvent dependency was observed in the reaction. However, no results surpassed that obtained in CH_2Cl_2 (Table 1, entries 6−11), which was then selected as the standard reaction media for further investigations.

Since the synthetic method of BoPhoz-type ligands is highly modular, the optimization of the BoPhoz skeleton was therefore performed.[6] After a systematic investigation of a number of BoPhoz-type ligands with varying electronic and steric properties, we determined that those with a trifluoromethyl group on the aryl ring of the aminophosphino moiety tended to give better results than those obtained with Me-BoPhoz in terms of reactivity and enantioselectivity (Table 1, entries 12−16). For instance, ligand **2b** with a CF_3 group on the 4-position of the aryl ring gave 92% ee and full conversions in the hydrogenation of ester **1a** (Table 1, entry 12). The introduction of two CF_3 groups onto the 3,5-position of the aryl ring also resulted in high enantioselectivity (Table 1, entry 14). In particular, new phosphine−aminophosphine ligand (S_C,R_{Fc},R_P)-**3**, bearing a stereogenic *P* center in the phosphino moiety and a 4-CF_3 group in the aryl ring of the aminophosphino moiety, provided the best result in terms of ee values and conversion (Table 1, entry 16). Lowering the H_2 pressure to 10 atm also provided good enantioselectivity (93% ee); however, an elevated temperature (50 °C) was required to complete the hydrogenation (entry 17). Ligand (S_C,R_{Fc},R_P)-**3** was synthesized according to the method developed by Chen et al. very recently, in which ferrocene-based *P*-chiral compounds can be easily prepared in a simple and highly stereoselective way.[7]

To demonstrate the flexibility of this method, the hydrogenation of a series of (*Z*)-3-aryl-4-phthalimidobut-2-enoates was studied with the Rh complex of (S_C,R_{Fc},R_P)-**3** under the optimized conditions (CH_2Cl_2 as the reaction media, H_2 pressure of 60 atm). As shown in Table 2, the hydrogenation proceeded to completion and provided the corresponding hydrogenated products with high enantioselectivities (93−97% ee). The results reveal that there is no major effect on the substitution pattern of the substituent on the aryl ring of substrates. For example, all three substrates with a methoxy group on the aryl ring were reduced in 94−96% ee (Table 2, entries 2−4). Among all substrates with para substituents tested, ethyl (*Z*)-3-(3-cyclopentoxy-4-methoxyphenyl)-4-phthalimidobut-2-enoate (**1i**) was hydrogenated with the best selectivities of 97% ee (Table 2, entry 9). Excellent enantioselectivity (97% ee) was observed in the hydrogenation of the substrate containing a thiophene-heteroaryl group. However, in this case, ligand **2b** exhibited better ee's than (S_C,R_{Fc},R_P)-**3** (Table 2, entry 12).

Table 2. Asymmetric Hydrogenation of Ethyl (*Z*)-4-Phthalimido-3-arylbut-2-enoate **1**[a]

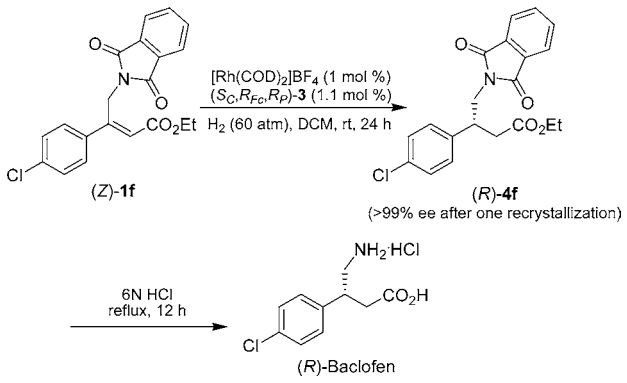


entry	substrate (Ar)	ee (%)
1	**1a**: Ar = Ph	95 (*R*)
2	**1b**: Ar = 2-$MeOC_6H_4$	96 (−)
3	**1c**: Ar = 3-$MeOC_6H_4$	94 (−)
4	**1d**: Ar = 4-$MeOC_6H_4$	94 (−)
5	**1e**: Ar = 4-FC_6H_4	96 (−)
6	**1f**: Ar = 4-ClC_6H_4	95 (*R*)
7	**1g**: Ar = 4-BrC_6H_4	94 (−)[b]
8	**1h**: Ar = 4-$CF_3C_6H_4$	93 (−)
9	**1i**: Ar = 3-cyclopentoxy-4-$MeOC_6H_3$	97 (*R*)
10	**1j**: Ar = 2-naphthyl	94 (−)
11	**1k**: Ar = 2-(6-methoxynaphthyl)	94 (−)
12	**1l**: Ar = 2-thiophenyl	97 (−)[b]

[a] All reactions were carried out with 0.25 mmol of substrate at room temperature under a H_2 pressure of 60 atm in 2 mL of CH_2Cl_2 for 24 h, with a substrate/$[Rh(COD)_2]BF_4$/(S_C,R_{Fc},R_P)-**3** ratio of 1/0.01/0.011. Full conversions were obtained in all reactions. The ee values were determined by HPLC on a chiral column (Chiralpak AD or Chiralcel OD-H). [b] The result was obtained with ligand **2b**.

To explore the potential synthetic versatility of this new method, we sought to apply it to the synthesis of a range of chiral pharmaceuticals using asymmetric hydrogenation as a key step. For this purpose, an enantioselective synthesis of (*R*)-baclofen serves as an example (Scheme 2). Baclofen is a lipophilic analogue of γ-aminobutyric acid, and it is widely used as an antispasmodic agent. Although baclofen is commercialized in its racemic forms, pharmacological

Scheme 2. Synthesis of (*R*)-Baclofen



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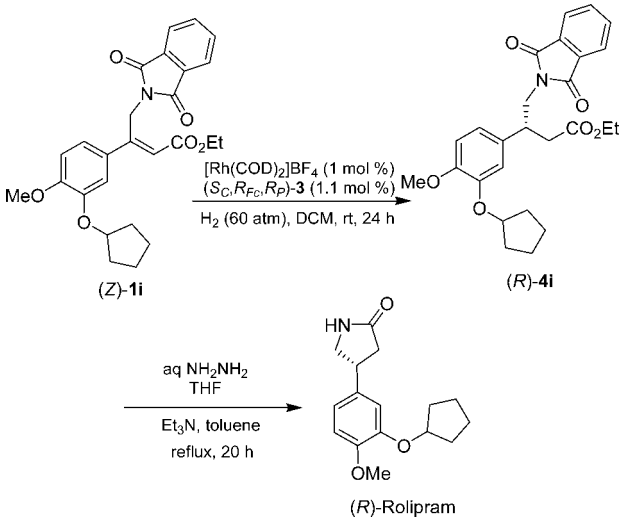
studies have shown that its biological activity resides exclusively in its (*R*)-enantiomer.[8] Therefore, several efforts have been made to prepare enantiomerically pure (*R*)-baclofen.[9] The requisite hydrogenation substrate, (*Z*)-3-(4-chlorophenyl)-4-phthalimidobut-2-enoate (**1f**), can be easily prepared from 4′-chloroacetophenone through a three-step transformation in good yields (over 60% in total yields) as shown in Scheme 1. With the catalysts generated in situ from $[Rh(COD)_2]BF_4$ and (S_C,R_{Fc},R_P)-**3**, *N*-phthaloyl-protected amino acid ester **4f** can be obtained in quantitative yield and good enantioselectivity (95% ee). Compound **4f** can be upgraded via recrystallization to over 99% ee (91% recovery). This was converted in one step to (*R*)-baclofen in nearly quantitative yield, demonstrating the potential utility of this method in the synthesis of chiral pharmaceuticals. Second, we applied this method to the synthesis of rolipram, which has been known as a selective inhibitor of PDE-IV, a cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase, and is employed as an anti-inflammatory agent and antidepressant.[10−11] For the synthesis of rolipram, **1i** was synthesized from the corresponding ketones and was hydrogenated with this new method in high enantioselectivity (97% ee). With deprotection with aqueous hydrazine followed by treatment with Et_3N in toluene at refluxing temperature, the hydrogenation product **4i** could be converted into (*R*)-rolipram in 78% yield (Scheme 3).

Scheme 3. Synthesis of (*R*)-Rolipram



In conclusion, we discovered that a series of chiral γ-amino acid esters could be synthesized in high enantioselectivity in the first Rh-catalyzed asymmetric hydrogenation of γ-phthalimido-α,β-unsaturated carboxylic acid esters using highly modular chiral BoPhoz-type phosphine−aminophosphine ligands. The method has been applied successfully to the synthesis of several pharmaceuticals including (*R*)-baclofen and (*R*)-rolipram with high enantioselectivities. The high crystallinity conferred by the phthalimido group provided a convenient way to upgrade the ee of the hydrogenated product to a very high level. It is our hope that this work will provide a new and practical method to prepare chiral γ-amino acids and their derivatives.

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Supporting Information Available: Experimental details, optimization data, spectra for new compounds, and analysis of ee's of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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